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(19) (CA) # CANADIAN PATENT

(54) METHOD FOR THE PRODUCTION OF 2-SUBSTITUTED ADENOSINE DERIVATIVE

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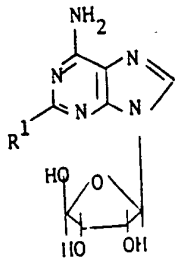
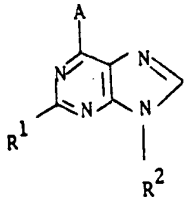
This invention relates to a method for the production of novel 2-substituted adenosine derivatives.

The invention provides a method for the production of 2-substituted adenosine derivatives of the formula (I)



(I)

wherein R^1 is a phenyl group or a phenyl group which has one or more substituents such as nitrol, halogen (e.g. fluorine, chlorine, bromine, iodine), alkyl (e.g. methyl, ethyl, n-propyl, iso-propyl, etc.) and alkoxy (e.g. methoxy, ethoxy, n-propoxy, iso-propoxy, etc.), which comprises allowing ammonia to react with a 2,6-disubstituted nebularine derivative of the formula (II)



(II)

wherein R^1 has the same meaning as defined above, R^2 is a ribosyl group or a ribosyl group whose hydroxyl groups are respectively protected by a protective group [such as an alkylidene group (e.g. iso-propylidene, ethoxymethylidene, etc.), an aralkylidene group (e.g. benzylidene, parachlorobenzylidene, etc.), carboxylic acid acyl group (e.g. acetyl, propionyl, valeryl, benzoyl, toluoyl, etc.) and an aralkyl group (e.g. benzyl, trityl, etc.)] and A is halogen such as chlorine, bromine, fluorine and iodine, a group which is represented by the formula $-S-R^3$ wherein R^3 is hydrogen, an alkyl group such as methyl, ethyl, n-propyl, iso-propyl, etc., or an aralkyl group such as benzyl, phenethyl, etc., and a group which is represented by the formula $-SO_nR^4$ wherein R^4 is hydroxyl, an alkyl or an aralkyl group as mentioned above and n is an integer of 1 or 2, and removing the protective group, if any, from the ribosyl group.

In accordance with this invention, 2,6-disubstituted nebularine derivative (II) is allowed to react with ammonia. Ammonia is in general used as an aqueous ammonia or alcoholic ammonia. Such an ammonia is used in the proportion of one equivalent or more, preferably about 2 to about 5 equivalents, relative to the 2,6-disubstituted nebularine derivative (II). The reaction generally proceeds at about 30° to about 200°C, favorably about 100° to about 200°C. In some cases, it is preferable to conduct the reaction in a sealed vessel under

heating and pressure. Suitable solvents are water, methanol, ethanol, 2-methoxyethanol and a mixture thereof.

The above reaction directly gives a 2-substituted adenosine derivative (I) when a group represented by R^2 of a 2,6-disubstituted nebularine derivative (II) is a non-protected ribosyl group or a ribosyl group protected with an acyl group. Protective groups other than acyl will remain attached to the ribosyl group even after the reaction, but those protective groups can be easily removed by per se known procedures. For example, 2',3'-O-alkylidene (e.g. isopropylidene, benzylidene, etc.) and trityl groups attached to the ribosyl group may be easily removed by heating(for instance, at about 50° to 70°C) under acid conditions (for instance, at pH of about 1.5 to about 2.5), and the benzyl group in the ribosyl group may be easily removed by per se known catalytic reduction.

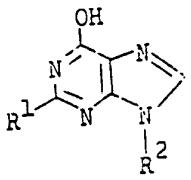
The reaction mixture is, for example, filtered, concentrated and recrystallized from a suitable solvent to isolate the desired end product in a high purity.

The end product of this invention is usually obtained in the form of the free base and, if required or desired, may be converted into their pharmaceutically acceptable acid addition salts such as the hydrochloride, sulfate, citrate, etc., by conventional procedures.

The 2-substituted adenosine derivatives thus obtained are novel compounds and have a prolonged coronary dilatory action and hypotensive action. Moreover, the pharmacological activity of these 2-substituted adenosine derivatives is

prolonged and substantially greater as compared with adenosine per se as well as other adenosine derivatives. Additionally, the present compounds are also substantially free of side-effects.

The starting material of this invention, 2,6-disubstituted nebularine derivatives (II), is also novel, which can be obtained by converting the 2-substituted inosine derivatives of the formula (III)



(III)

wherein R^1 and R^2 have the same meaning as defined above, to the compounds (II) by per se conventional means.

When all the hydroxyl groups in the group R^2 in the compound (III) are not protected, the remaining non-protected hydroxyl groups must be protected with the above-described protective groups, and then, the hydroxyl group at 6-position of the purine nucleus is substituted with the group A by per se conventional methods.

To obtain the compound (II) wherein the group A is a halogen, the inosine derivative (III) is for instance subjected to reaction with a halogenating agent such as phosphorus oxyhalide (e.g. phosphorus oxychloride, phosphorus oxybromide, pyrophosphoryl chloride), phosphorus halides (e.g. phosphorus pentachloride, etc.), or and thionyl halide (e.g. thionyl chloride, thionyl bromide, etc.) in the presence of an acid acceptor such as pyridine, triethylamine, dimethylaniline,

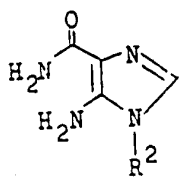
diethylaniline, or with Vilsmeier-Haack reagent [A. Vilsmeier and A. Haack, Ber. 60, 119(1927)].

To obtain the 6-mercapto derivative, for instance, a phosphorus sulfide such as diphosphorus pentasulfide, tetraphosphorus heptasulfide, etc., is allowed to react with an inosine derivative (III) in the presence of an acid acceptor such as pyridine, trimethylamine, triethylamine, etc. Reaction of an alkyl halide (e.g. methyl iodide, ethyl bromide, propyl bromide, etc.) or aralkyl halide (e.g. benzyl chloride, phenethyl bromide) with the 6-mercapto derivative gives the 6-alkyl or aralkyl mercapto derivative.

The above 6-mercapto derivative, or 6-alkyl or aralkyl mercapto derivative is subjected to oxidation, by per se conventional methods, for instance, it is allowed to react with an oxidating agent such as hydrogen peroxide, chlorine, etc., whereby there is obtained the compound (II) in which A is a group represented by the formula $-SO_nR^4$ wherein R^4 and n have the same meaning as defined above.

After the above introduction of the group A, the protective groups of the ribosyl group may be removed.

2-Substituted inosine derivatives (III) are also new compounds. These compounds are obtained by reacting an imidazole derivatives of the formula (IV)



(IV)

wherein R^2 has the same meaning as defined above, with an ester of a carboxylic acid of the formula (V)

$$R^1COOH \qquad (V)$$

wherein R^1 has the same meaning as defined above, in the presence of an alkali metal alcoholate.

The ester is exemplified by alkyl (e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, n-amyl, etc.), aryl (e.g. phenyl, naphthyl, etc.) or aralkyl (e.g. benzyl, etc.) ester of the carboxylic acid (V). Such an ester is used in the proportion of not less than an equivalent relative to the imidazole derivative (IV), and is desirably used in an amount of about 5 to about 10 mols relative to the imidazole derivative (IV).

Examples of the alkali metal alcoholate include sodium methylate, lithium methylate, sodium ethylate, sodium methoxyethylate, potassium tert.-butylate and the like. It is expedient to employ the alcoholic solution of alkali metal alcoholate which is obtained by reacting an alkali metal with a large excess of alkanol. It is desirable to use at least about 10 equivalents of the alkali metal alcoholate relative to the imidazole derivative (IV). This reaction advantageously proceeds in the presence of a suitable solvent. As the solvent , for example, alkanols such as methanol, ethanol, propanol, 2-methoxyethanol, 2-ethoxyethanol and the like are advantageously used. The reaction may be accelerated by heating the reaction system to a temperature near the boiling point of the solvent used. The resulting 2-substituted inosine

derivative (III) substituted by, at 2-position, the phenyl group due to the ester of the carboxylic acid (V) can be easily recovered from the reaction mixture. For instance, 2-substituted inosine derivative (III) may be isolated in high purity and in good yield by the step of neutralizing the reaction mixture, concentrating it and recrystallizing the resulting crude crystals from, for example, water or aqueous alkanol and the like.

In the following references and examples, the relationship between part(s) by weight and part(s) by volume corresponding to the relationship between gram(s) and milliliter(s). The references relate to the production of intermediates and starting materials of formulae II and III, whereas the examples relate to the preparation of formula I compounds from formula II compounds.

Reference 1

In 400 parts by volume of 1.23N sodium methylate is dissolved 12.7 parts by weight of 5-amino-1-β-D-ribofuranosyl-4-imidazole carboxyamide (hereinafter referred to briefly as AICA-riboside) and 20 parts by volume of ethyl benzoate is added dropwise under reflux and stirring. The mixture is heated under reflex for 4 hours and poured into 500 parts by volume of ice-water. The mixture is adjusted to pH 3 with concentrated hydrochloric acid and, then, allowed to stand for a while, whereupon 5.2 parts by weight of colorless needles of 2-phenylinosine are obtained. m.p. 225°-230°C. $[\alpha]_D^{22} = -13.0°$ (C=1.0, 0.1N-NaOH)

Ultraviolet absorption (mμ)

λ_{max}^{PH2} 261 (ε = 12,700), 289 (ε = 13,900)

λ_{max}^{PH13} 235 (ε = 27,000), 264 (ε = 14,800), 283(ε=13,400)

Elementary analysis	C(%)	H(%)	N(%)
Calculated for $C_{16}H_{16}N_4O_5$	55.81	4.68	16.27
Found	55.26	4.63	16.28

Reference 2

To 200 parts by volume of 2-methoxyethanol dissolving 10 parts by weight of metallic sodium are added 10.0 parts by weight of AICA-riboside and 15 parts by volume of ethyl-p-methoxybenzoate, and then the reaction mixture is heated under reflux for 30 minutes. After cooling, the reaction mixture is poured into 400 parts by volume of water and adjusted to pH 7.5 with concentrated hydrochloric acid, whereupon needles of 2-(p-methoxyphenyl)-inosine are obtained. The crystals are washed with 100 parts by volume of water, and are left standing overnight at 70°C over phosphorus pentoxide. The yield of the product is 11.2 parts by weight. m.p. 242°C (decomp.)

Elementary analysis	C(%)	H(%)	N(%)
Calculated for $C_{17}H_{18}N_4O_6 \cdot \frac{1}{2}H_2O$	53.26	5.00	14.62
Found	52.72	4.97	14.46

Ultraviolet absorption

$\lambda_{max}^{0.1N\text{-}HCl}$ 300 mμ (ε =19,900), 264 mμ

$\lambda_{min}^{0.1N\text{-}HCl}$ 237 mμ, $\lambda_{max}^{H_2O}$ 299 mμ (ε =18,800), 259 mμ (ε =13,000) $\lambda_{min}^{H_2O}$ 235 mμ, $\lambda_{max}^{0.1N\text{-}NaOH}$ 285mμ (ε =15,800), 267 mμ, 248 mμ (ε =19,100)

$\lambda_{min}^{0.1N\text{-}NaOH}$ 260 mμ, 228 mμ.

Reference 3

In 250 parts by volume of pyridine is suspended 52 parts by weight of 2-(p-methoxy phenyl)inosine, and thereto 250 parts by volume of acetic anhydride are added dropwise. After stirring for about 2 hours at room temperature, the reaction mixture is dried up under reduced pressure. The residue is dissolved in 500 parts by volume of chloroform, and washed with 0.1N hydrochloric acid, 5% by weight of aqueous solution of sodium bicarbonate and water in turn. The chloroform layer is dried over anhydrous sodium sulfate. To the chloroform solution are added 15 parts by volume of dimethylformamide and 45 parts by volume of thionyl chloride in turn, and the mixture is heated under reflux for 3 hours. The mixture is concentrated to dryness under reduced pressure, and the residue is dissolved in 250 parts by volume of chloroform. The solution is washed with water, 0.1N hydrochloric acid and 5% by weight of an aqueous solution of sodium bicarbonate in turn, and the chloroform layer is dried over anhydrous sodium sulfate. This solution is adsorbed on column chromatography with silica gel (500 parts by weight of silica gel), and is eluated with 2,000 parts by volume of chloroform containing 2% methanol. The eluate is concentrated to dryness under reduced pressure, and the resultant is recrystallized from 100 parts by volume of methanol, whereby 61 parts by weight of colorless needles of 2-(p-methoxyphenyl)-6-chloro-2',3',5'-tri-o-acetylnebularine are obtained. m.p. 134.5°-135.5°C.

Elementary analysis	C(%)	H(%)	N(%)	Cl(%)
Calculated for $C_{23}H_{25}N_4O_8Cl$	52.23	4.47	10.80	6.83
Found	52.26	4.62	10.73	6.65

Ultraviolet absorption

λ_{max}^{MeOH} 240 mμ (ε =14,200), 295 mμ (ε =20,600),
312 mμ (ε =21,000)

Reference 4

From 5 parts by weight of AICA-riboside, 180 parts by volume of 1N sodium methoxyethylate and 9 parts by weight of methyl 3,4,5-tri-methoxybenzoate, are obtained 2,3 parts by weight of needles of 2-(3,4,5-tri-methoxyphenyl)-inosine in a manner similar to that described in Reference 1. m.p. 210°C.

Elementary analysis	C(%)	H(%)	N(%)
Calculated for $C_{19}H_{22}N_4O_8 \cdot H_2O$	50.44	5.35	12.38
Found	50.21	4.85	11.96

Reference 5

In 200 parts by volume of pyridine are dissolved 25 parts by weight of 2-(p-methoxyphenyl)inosine, and thereto are added 200 parts by volume of acetic anhydride.

After stirring for 2 hours at room temperature, the reaction mixture is concentrated to dryness, and the residue is dissolved in 300 parts by volume of chloroform. The chloroform layer is washed with 0.1N hydrochloric acid, 5% by weight of an aqueous solution of sodium bicarbonate and water in turn, and the chloroform layer is dried up.

The residue is dissolved in 800 parts by volume of pyridin and thereto is added 60 parts by weight of diphosphorus pentasulfide, followed by heating under reflux for 5 hours. The mixture is poured into 2000 parts by volume of ice-water. After stirring for 3 hours, a precipitate is filtrated. The precipitate is dissolved in chloroform, the insoluble product is filtrated and, the residue is concentrated to dryness and is dissolved in 300 parts by volume of 50% aqueous methanol. The mixture is added to 150 parts by volume of 2N sodium hydroxide and 25 parts by volume of ethyl iodide, and stirred for 20 hours at room temperature, whereby 13 parts by weight of needles of 2-(p-methoxyphenyl)-6-ethylthionebularine m.p. 155°-157°C.

Elementary analysis	C(%)	H(%)	N(%)
Calculated for $C_{19}H_{22}N_4O_5S$	54.54	5.28	13.39
Found	54.13	5.13	13.07

Example 1

In 32 parts by volume of pyridine is dissolved 3.2 parts by weight of 2-phenylinosine, followed by the addition of 16 parts by volume of acetic anhydride. The mixture is stirred at 50°C for 5 hours and concentrated to dryness under reduced pressure. The syrupy residue is dissolved in 30 parts by volume ethanol and the solution is allowed to stand in a refrigerator, whereupon crystals separate out. The crystals are recovered by filtration and recrystallized from ethanol, whereupon 3.625 parts by weight of colorless crystals of 2',3',5-tri-o-acetyl-2-phenyl-inosine are obtained.

m.p.146°-148°C.

Elementary analysis	C(%)	H(%)	N(%)
Calculated for $C_{22}H_{22}N_4O_8$	56.17	4.71	11.91
Found	56.09	4.50	11.68

$[\alpha]_D^{25}$=-16.5° (C=1.02, dimethylformamide)

Ultraviolet absorption : $\lambda_{max}^{C_2H_5OH}$ 300 mμ (ε =12,200)

To 20 parts by volume of chloroform there are added 1.5 part by volume of dimethylformamide and 4.5 parts by volume of thionyl chloride. The mixture is allowed to stand for 30 minutes, at the end of which time 6 parts by weight of the above 2',3',5'-tri-o-acetyl-2-phenylinosine is added. The mixture is boiled for 7 hours and, then, concentrated to dryness. The concentrate is dissolved in 200 parts by volume of chloroform and washed with 100 parts by volume of water. The chloroform layer is concentrated to dryness and, under cooling, the syrupy residue is dissolved in 300 parts by volume of 20% methanolic ammonia. The solution is allowed to stand in a refrigerator for 20 hours and, then, concentrated to dryness. The residue is recrystallized from methanol to obtain 3.5 parts by weight pale yellowish needles of 2-phenyl-6-chloronebularine

m.p.204°-207°C (decomp.)

Elementary analysis	C(%)	H(%)	N(%)	Cl(%)
Calculated for $C_{16}H_{15}N_4O_4Cl$	52.97	4.17	15.44	9.7
Found	52.82	4.09	15.58	9.5

Two parts by weight of 2-phenyl-6-chloronebularine and 150 par by volume of 20% methanolic ammonia are heated in an autoclave

at 150°C for 5 hours and, after cooling, the reaction mixture is concentrated. The concentrate is recrystallized from water to obtain 1.6 part by weight of colorless needles of 2-phenyl adenosine, m.p. 228°-230°C.

The $[\alpha]_D$ and ultraviolet absorption spectrum of this product are in agreement with those of product obtained in Example 2. Mixture-melting with the product of Example 2 results in no melting point depression.

Example 2

In 200 parts by volume of pyridine is dissolved 3.145 parts by weight of 2',3',5'-tri-o-acetyl-2-phenylinosine, followed by the addition of 7.5 parts by weight of phosphorus pentasulfide and 0.35 parts by volume of water. Under stirring, the mixture is refluxed for 6.5 hours. The reaction mixture is concentrated to dryness under reduced pressure and 300 parts by volume of water is added to the residue, followed by extraction with 200 parts by volume of chloroform. The chloroform layer is washed with water, 0.5N hydrochloric acid and water in the order mentioned, dried over anhydrous sodium sulfate and concentrated under reduced pressure. To the produced syrupy residue, 120 parts by volume of 20% methanolic ammonia is added. The mixture is allowed to stand overnight in a refrigerator and, then, a concentrated under reduced pressure, whereupon a colorless powder separates. The powder is recovered by filtration and recrystallized from 300 parts by volume of water. The procedure gives

1.576 part by weight of pale yellowish needles of 2-phenyl-6-mercaptoinosine. m.p. 180°C.

Elementary analysis	C(%)	H(%)	N(%)	S(%)
Calculated for $C_{16}H_{16}N_4O_4S \cdot H_2O$	50.78	4.79	14.81	8.49
Found	51.01	4.76	14.70	8.68

$[\alpha]_D^{25} = -25.9^\circ$ (C=0.87, dimethylformamide)

Ultraviolet absorption:

$\lambda_{max}^{0.1N\text{-HCl}}$ 324 mμ (ε =22,700), 253 mμ;

$\lambda_{max}^{H_2O}$ 324 mμ (ε =24,900), 251 mμ;

$\lambda_{max}^{0.1N\text{-NaOH}}$ 312 mμ (ε=18,900), 262 mμ (ε=23,300)

In 30 parts by volume of 0.1N sodium hydroxide is dissolved 1.134 part by weight of 2-phenyl-6-mercaptoinosine (containing 1 molecule of water), followed by the addition of 0.48 part by weight of methyl iodide and 2 parts by volume of ethanol. The mixture is stirred at room temperature for 3 hours, whereupon a colorless precipitate is obtained. The precipitate is recovered by filtration and recrystallized from 750 parts by volume of water. The procedure gives 0.804 part by weight of colorless crystals of 2-phenyl-6-methylthioinosine. m.p. 205°C.

Elementary analysis	C(%)	H(%)	N(%)	S(%)
Calculated for $C_{17}H_{18}N_4O_4S$	54.53	4.85	14.97	8.56
Found	54.51	4.75	14.84	8.58

To 0.5 part by weight of 2-phenyl-6-methylthioinosine is added 5 parts by volume of 20% methanolic ammonia, and the mixture is heated in a sealed vessel at 180°C for 20 hours.

After cooling, the reaction mixture is concentrated to dryness under reduced pressure and the residue is recrystallized from 30 parts by volume of water. The procedure gives colorless needles of 2-phenyladenosine. m.p.225°C-228°C.

Elementary analysis	C(%)	H(%)	N(%)
Calculated for $C_{16}H_{17}O_4N_5$	55.97	4.99	20.40
Found	55.72	4.81	20.30

Mass spectrum ($C_{16}H_{17}O_4N_5$=343):

m/e =343(molecular ion peak), 326, 313, 270, 226, 254, 240, 224, 212, 211, 195, 104

Example 3

A mixture of 15 parts by weight of 2-(p-methoxyphenyl)-6-chloro-2',3',5'-tri-o-acetyl nebularine and 150 parts by volume of 20% methanolic ammonia is heated at 180°C for 10 hours in a sealed vessel. After cooling, the reaction mixture is concentrated to about 100 parts by volume, and then is left standing for 4 hours in a refrigerator, followed by filtration of the crystals obtained. The crystals are washed with a little amount of methanol and ether, and are dried for 2 hours at 180°C over phosphorus pentaoxide. The product is recrystallized from 1000 parts by volume of 50% methanol, whereby 9.0 parts by weight of colorless needles of 2-(p-methoxyphenyl)adenosine are obtained. m.p.250°C.

Elementary analysis	C(%)	H(%)	N(%)
Calculated for $C_{17}H_{19}N_5O_5$	54.68	5.13	18.76
Found	54.67	4.97	18.35

Ultraviolet absorption spectrum

$\lambda_{max}^{H_2O}$ 253 mμ (ε=19,300), 289 mμ (ε=17,500)
274 mμ (ε=14,400), 306 mμ (ε=18,600)

Example 4

To 1.3 part by weight of 2-(3,4,5-trimethoxyphenyl)-inosine dissolved in 10 parts by volume of pyridine, 5 parts by volume of acetic anhydride is added. After standing for 20 hours at room temperature, the mixture is concentrated to dryness under reduced pressure. Ethanol is added to the residue and the residue is ground into powder followed by filtration, whereby 1.6 part by weight of colorless crystals of 2',3',5'-tri-o-acetyl-2-(3,4,5-trimethoxyphenyl)inosine are obtained.

To a mixture of 0.4 part by volume of dimethylformamide, 1.1 part by weight of thionyl chloride and 5 parts by volume of chloroform, are added 1.6 part by weight of 2',3',5'-tri-o-acetyl-2-(3,4,5-trimethoxyphenyl)inosine, and is heated under reflux for 7 hours. After being concentrated to dryness, the mixture is dissolved in 50 parts by volume of chloroform.

After being washed with 50 parts by volume of aqueous solution, the chloroform layer is concentrated to dryness. The residue is dissolved in 20 parts by volume of 20% methanolic ammonia, and is heated for 8 hours at 180°C in

a sealed vessel. The reaction mixture is concentrated to dryness. The residue is dissolved in chloroform. The chloroform solution is subjected to column-chromatography with 12 parts by weight of silica gel (0.05-2mm) (the solvent of development: chloroform:methanol=9:1), whereby 0.13 part by weight of 2-(3,4,5-trimethoxyphenyl)adenosine is obtained as needles. m.p.99°-101°C.

Elementary analysis	C(%)	H(%)	N(%)
Calculated for $C_{19}H_{23}N_5O_7$	51.57	5.47	15.83
Found	51.41	5.41	16.19

Ultraviolet absorption spectrum

$\lambda_{max}^{H_2O}$ 221 mμ, 260 mμ, 295 mμ

$\lambda_{min}^{H_2O}$ 244 mμ, 269 mμ

Example 5

In 80 parts by volume of 30% methanolic ammonia is dissolved 10 parts by weight of 2-(p-methoxyphenyl)-6-ethylthionebularine, and is heated under reflux for 20 hours at 180°C. in a sealed vessel, followed by treatment in a manner similar to that described in Example 3, whereby 7.5 parts by weight of 2-(p-methoxyphenyl)adenosine is obtained.

Elementary analysis	C(%)	H(%)	N(%)
Calculated for $C_{17}H_{19}O_5N_5$	54.68	5.13	18.76
Found	54.48	5.12	18.78

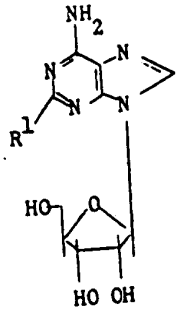
Ultraviolet absorption spectrum

$\lambda_{max}^{H_2O}$ 253 mμ, 289 mμ

$\lambda_{max}^{0.1N\text{-}HCl}$ 274 mμ, 306 mμ

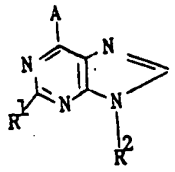
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A method for the production of a 2-substituted adenosine derivative of the formula (I);



(I)

wherein R^1 is a phenyl group or a phenyl group which has one or more substituents selected from the group consisting of nitro, halogen, alkyl and alkoxy, which comprises allowing ammonia to react with a 2,6-disubstituted nebularine derivative of the formula (II)



(II)

wherein R^1 has the same meaning as defined above, R^2 is a ribosyl group or a ribosyl group whose hydroxyl groups are protected by a protective group, and A is halogen, a group represented by the formula $-S-R^3$ wherein R^3 is hydrogen, alkyl or aralkyl group or $-SO_nR^4$ wherein R^4 is hydroxyl group, alkyl or aralkyl group and n is an integer of 1 or 2, and removing the protective group, if any, from the ribosyl group.

2. A method as claimed in claim 1 wherein R^1 is phenyl.

3. A method as claimed in claim 1 wherein R^1 is paramethoxyphenyl.

4. A method as claimed in claim 1 for the production of 2-phenyl adenosine which comprises reacting 2-phenyl-6-chloronebularine with ammonia.

5. A method as claimed in claim 4 wherein 2-phenyl-6-chloronebularine

C

is heated under pressure with 20% methanolic ammonia.

6. A method as claimed in claim 1 for the production of 2-phenyl adenosine which comprises reacting 2-phenyl-6-methylthioinosine with ammonia.

7. A method as claimed in claim 6 wherein 2-phenyl-6-methylthioinosine is heated under pressure with 20% methanolic ammonia.

8. A method as claimed in claim 1 for the production of 2-(p-methoxyphenyl)adenosine which comprises reacting 2-(p-methoxyphenyl)-6-chloro-2',3',5'-tri-o-acetyl nebularine with ammonia.

9. A method as claimed in claim 8 wherein 2-(p-methoxyphenyl)-6-chloro-2',3',5'-tri-o-acetyl nebularine is heated under pressure with 20% methanolic ammonia.

10. A method as claimed in claim 1 for the production of 2-(3,4,5-trimethoxyphenyl)adenosine which comprises reacting 2',3',5'-tri-o-acetyl-2-(3,4,5-trimethoxyphenyl)-6-chloro-nebularine with ammonia.

11. A method as claimed in claim 10 wherein 2',3',5'-tri-o-acetyl-2-(3,4,5-trimethoxyphenyl)-6-chloro-nebularine is heated under pressure with 20% methanolic ammonia.

12. A method as claimed in claim 1 for the production of 2-(p-methoxyphenyl)adenosine which comprises reacting 2-(p-methoxyphenyl)-6-ethylthionebularine with ammonia.

13. A method as claimed in claim 12 wherein 2-(p-methoxyphenyl)-6-ethylthionebularine is heated under pressure with 30% methanolic ammonia.